Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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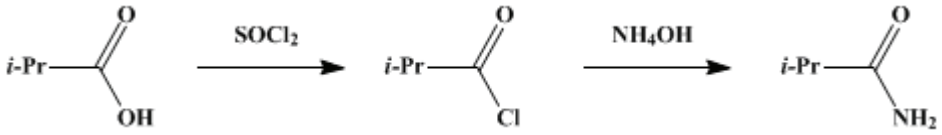
ISOBUTYRAMIDE



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1. Procedure

A. *Isobutyryl chloride*. A 1-l. three-necked flask is equipped with a 250-ml. dropping funnel, an efficient stirrer sealed with a glycerol-lubricated rubber tube, and an efficient condenser (Note 1). The water supplied to the condenser is cooled to 0°, and the flask is cooled in a large water bath. The apparatus is set up in a hood, and a gas-absorption trap is attached to the top of the condenser.

In the flask is placed 542 g. (4.55 moles) of thonyl chloride; to this is added dropwise, and with rapid stirring, 352 g. (4 moles) of isobutyric acid (Note 2). A vigorous evolution of hydrogen chloride and sulfur dioxide takes place. When all the acid has been added, the water bath is heated to 80° and is kept at this temperature for 30 minutes. Stirring is continued throughout the heating. The reaction mixture is then distilled through a 30-cm. Vigreux column by means of an oil bath heated on a hot plate (Note 3). The fore-run boiling up to 89° weighs 44 g. The isobutyryl chloride which is collected at 89–93° weighs 351 g. The residue weighs 49 g. On combining the fore-run and residue and redistilling slowly, an additional 33 g. of isobutyryl chloride is obtained; the total yield is 384 g. (90%). Redistillation gives a faintly yellow product boiling at 90–92° (Note 4) and (Note 5).

B. *Isobutyramide*. In a 3-l. flask, equipped with an efficient stirrer and a 500-ml. dropping funnel, and surrounded by an ice-salt freezing mixture, is placed 1.25 l. of cold concentrated aqueous ammonia (about 28%). To this 318 g. (3 moles) of isobutyryl chloride is added dropwise with rapid stirring at such a rate that the temperature of the reaction mixture does not rise above 15°, and the evolution of white fumes (mostly ammonium chloride) does not become vigorous. Stirring is continued for 1 hour after the addition of the acid chloride is finished.

The flask is heated by steam in a large can, and the reaction mixture is evaporated to dryness under reduced pressure (Note 6). The dry residue of ammonium chloride and isobutyramide is boiled 10 minutes with 2 l. of dry ethyl acetate, and the boiling solution is filtered quickly through a fluted filter paper on a large hot funnel. The residue on the filter is extracted in the same way with two 1-l. portions of ethyl acetate. The combined ethyl acetate extracts are cooled to 0°, and the crystalline amide which separates is removed by filtration. The filtrate is concentrated to about 300 ml. and chilled, and a second crop of amide is collected (Note 7) and (Note 8). The two crops of isobutyramide are combined and dried, first in an oven at 70° for 3 hours and then in a vacuum desiccator. The yield of glistening white needles melting at 127–129° is 203–215 g. (78–83%) (Note 9). This material is suitable for the preparation of isobutyronitrile.

2. Notes

1. A Friedrichs condenser is recommended. This efficient condenser has an inner cooling coil around which the vapors pass and condense. The submitters used rubber stoppers throughout.
2. Eastman's technical grade of isobutyric acid was distilled, and the fraction boiling at 151–153° was used.
3. The submitters used an electrically heated oil bath.
4. When 5 moles of thionyl chloride and 4 moles of isobutyric acid were used, the yield on the first distillation was 83%, and redistillation of the fore-run gave an additional 7%. There was practically no high-boiling material.

5. The submitters obtained the same percentage yields in runs four times as large.
6. The steam can should be large enough to contain the entire reaction flask; otherwise the evaporation is very slow.
7. If the mixture of amide and ammonium chloride is not thoroughly dry, the ethyl acetate removed at this point will contain water and must be dried and redistilled before further use.
8. The filtrate from the second crop of amide may be evaporated to dryness and the residue crystallized from a mixture of ethyl acetate and ligroin (60–68°). It is profitable to work up this third crop of amide only when the mother liquors from several runs are combined.
9. The submitters obtained the same percentage yield in runs twice as large.

3. Discussion

Isobutyramide has been prepared by the action of concentrated aqueous ammonia on isobutyryl chloride [1] or methyl isobutyrate; [2] by the action of liquid ammonia on ethyl isobutyrate; [3] by the Willgerodt reaction with aqueous ammonium polysulfide; [4] by distillation of ammonium isobutyrate [5] or a mixture of isobutyric acid and potassium thiocyanate; [6] by hydrolysis of isobutyronitrile; [7] and from the ozonolysis of 2,3-dimethyl-6-isopropylpyridine. [8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 436

References and Notes

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2. Meyer, *Monatsh.*, **27**, 43 (1906).
3. Hauser, Levine, and Kibler, *J. Am. Chem. Soc.*, **68**, 26 (1946).
4. King and McMillan, *J. Am. Chem. Soc.*, **68**, 1369 (1946).
5. Hofmann, *Ber.*, **15**, 982 (1882).
6. Letts, *Ber.*, **5**, 671 (1872).
7. Hoffmann and Barbier, *Bull. soc. chim. Belg.*, **45**, 565 (1936) [*C. A.*, **31**, 919 (1937)].
8. Lochte, Barton, Roberts, and Bailey, *J. Am. Chem. Soc.*, **72**, 3007 (1950).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ligroin

thonyl chloride

ammonium polysulfide

hydrogen chloride (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ammonium chloride (12125-02-9)

thionyl chloride (7719-09-7)

sulfur dioxide (7446-09-5)

potassium thiocyanate (333-20-0)

ethyl isobutyrate (97-62-1)

isobutyryl chloride (79-30-1)

Isobutyramide (563-83-7)

isobutyric acid (79-31-2)

Isobutyronitrile (78-82-0)

methyl isobutyrate (547-63-7)

ammonium isobutyrate (22228-82-6)

2,3-dimethyl-6-isopropylpyridine

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